Efavirenz versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes: A prospective study of HIV-positive individuals

Cain, Lauren E ; Caniglia, Ellen C ; Phillips, Andrew ; Olson, Ashley ; Muga, Roberto ; Pérez-Hoyos, Santiago ; Abgrall, Sophie ; Costagliola, Dominique ; Rubio, Rafael ; Jarrín, Inma ; Bucher, Heiner ; Fehr, Jan ; van Sighem, Ard ; Reiss, Peter ; Dabis, François ; Vandenhende, Marie-Anne ; Logan, Roger ; Robins, James ; Sterne, Jonathan A C ; Justice, Amy ; Tate, Janet ; Touloumi, Giota ; Paparizos, Vasilis ; Esteve, Anna ; Casabona, Jordi ; Seng, Rémonie ; Meyer, Laurence ; Jose, Sophie ; Sabin, Caroline ; Hernán, Miguel A ; et al

Abstract: OBJECTIVE To compare regimens consisting of either ritonavir-boosted atazanavir or efavirenz and a nucleoside reverse transcriptase inhibitor (NRTI) backbone with respect to clinical, immunologic, and virologic outcomes. DESIGN Prospective studies of human immunodeficiency virus (HIV)-infected individuals in Europe and the United States included in the HIV-CAUSAL Collaboration. METHODS HIV-positive, antiretroviral therapy-naive, and acquired immune deficiency syndrome (AIDS)-free individuals were followed from the time they started an atazanavir or efavirenz regimen. We estimated an analog of the "intention-to-treat" effect for efavirenz versus atazanavir regimens on clinical, immunologic, and virologic outcomes with adjustment via inverse probability weighting for time-varying covariates. RESULTS A total of 4301 individuals started an atazanavir regimen (83 deaths, 157 AIDS-defining illnesses or deaths) and 18,786 individuals started an efavirenz regimen (389 deaths, 825 AIDS-defining illnesses or deaths). During a median follow-up of 31 months, the hazard ratios (95% confidence intervals) were 0.98 (0.77, 1.24) for death and 1.09 (0.91, 1.30) for AIDS-defining illness or death comparing efavirenz with atazanavir regimens. The 5-year survival difference was 0.1% (95% confidence interval: -0.7%, 0.8%) and the AIDS-free survival difference was -0.3% (-1.2%, 0.6%). After 12 months, the mean change in CD4 cell count was 20.8 (95% confidence interval: 13.9, 27.8) cells/mm lower and the risk of virologic failure was 20% (14%, 26%) lower in the efavirenz regimens. CONCLUSION Our estimates are consistent with a smaller 12-month increase in CD4 cell count, and a smaller risk of virologic failure at 12 months for efavirenz compared with atazanavir regimens. No overall differences could be detected with respect to 5-year survival or AIDS-free survival.

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Efavirenz versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes

A prospective study of HIV-positive individuals

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Abstract

Objective: To compare regimens consisting of either ritonavir-boosted atazanavir or efavirenz and a nucleoside reverse transcriptase inhibitor (NRTI) backbone with respect to clinical, immunologic, and virologic outcomes.

Design: Prospective studies of human immunodeficiency virus (HIV)-infected individuals in Europe and the United States included in the HIV-CAUSAL Collaboration.

Methods: HIV-positive, antiretroviral therapy-naive, and acquired immune deficiency syndrome (AIDS)-free individuals were followed from the time they started an atazanavir or efavirenz regimen. We estimated an analog of the "intention-to-treat" effect for efavirenz versus atazanavir regimens on clinical, immunologic, and virologic outcomes with adjustment via inverse probability weighting for time-varying covariates.

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*The contributors to the HIV-CAUSAL Collaboration are listed at the end of the article.**

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Andrew Phillips received fees for speaking from Gilead Sciences, consulting from GSK Biologicals, and advisory board membership from AbbVie.

Sophie Abgrall is a member of Janssen-Cilag board, received travel/accommodations for meeting from Gilead, Janssen-Cilag, ViiV.

Dominique Costagliola was a member of the French Gilead HIV board up to 2015. In the past 3 years, she gave lectures for Janssen-Cilag, Merck-Sharp & Dohme-Chibret, ViiV and received travel/accommodations/meeting expenses from Gilead, ViiV, Janssen-Cilag. She conducted post-marketing studies for Janssen-Cilag, Merck-Sharp & Dohme-Chibret and ViiV. She is currently a consultant of Innavirvax.

Rafael Rubio has acted as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Janssen and has received payment for talks from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Roche, and ViiV Healthcare.

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Jan Fehr was a member of the advisory boards for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, ViiV-Healthcare and has also received travel grants, educational grants and research grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Pfizer, Roche, ViiV-Healthcare. He is a member of the Swiss Federal Commission for Sexual Health.

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Caroline Sabin is a member of the speakers' bureau for Gilead Sciences. She provides educational training materials for Gilead Sciences, ViiV Healthcare and Janssen-Cilag. She is a member of Data Safety and Advisory Boards for Janssen-Cilag and ViiV Healthcare and has given talks for Bristol Myers Squibb.

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Results: A total of 4301 individuals started an atazanavir regimen (83 deaths, 157 AIDS-defining illnesses or deaths) and 18,786 individuals started an efavirenz regimen (389 deaths, 825 AIDS-defining illnesses or deaths). During a median follow-up of 31 months, the hazard ratios (95% confidence intervals) were 0.98 (0.77, 1.24) for death and 1.09 (0.91, 1.30) for AIDS-defining illness or death comparing efavirenz with atazanavir regimens. The 5-year survival difference was 0.1% (95% confidence interval: −0.7%, 0.8%) and the AIDS-free survival difference was −0.3% (−1.2%, 0.6%). After 12 months, the mean change in CD4 cell count was 20.8 (95% confidence interval: 13.9, 27.8) cells/mm^3 lower and the risk of virologic failure was 20% (14%, 26%) lower in the efavirenz regimens.

Conclusion: Our estimates are consistent with a smaller 12-month increase in CD4 cell count, and a smaller risk of virologic failure at 12 months for efavirenz compared with atazanavir regimens. No overall differences could be detected with respect to 5-year survival or AIDS-free survival.

Abbreviations: AIDS = acquired immune deficiency syndrome, ANRS = Agence Nationale de Recherches sur le SIDA, INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

Keywords: atazanavir, efavirenz, HIV, mortality, observational studies

1. Introduction

Until recently, most clinical guidelines for human immunodeficiency virus (HIV)-positive individuals recommended 1st-line regimens consisting of either a ritonavir-boosted protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs). One of the most commonly prescribed boosted PIs was atazanavir and one of the most commonly prescribed NNRTIs was efavirenz. The European acquired immune deficiency syndrome (AIDS) Clinical Society, the Department of Health and Human Services, and the International AIDS Society USA Panel all currently recommend atazanavir and efavirenz equally while the British HIV Association recommends atazanavir over efavirenz.[1–4] However, in the most recent Department of Health and Human Services guidelines, both atazanavir and efavirenz were moved from recommended to alternative in favor of integrase strand transfer inhibitors (INSTIs) and darunavir. The World Health Organization recommends efavirenz as part of 1st-line therapy and atazanavir as part of 2nd-line therapy.[5] In resource-limited settings, efavirenz and atazanavir remain cornerstones of antiretroviral therapy.

The comparative effectiveness of regimens based on ritonavir-boosted atazanavir and efavirenz is, however, incomplete. Two randomized clinical trials[6,7] and 3 observational studies[8–10] studied short-term virologic and immunologic outcomes with inconclusive results. All these studies were relatively small and few had follow-up times sufficient for the assessment of clinical outcomes such as death and AIDS-defining illness.

Here we examine clinical, immunologic, and virologic outcomes among AIDS-free individuals who started a 1st-line regimen consisting of either efavirenz or ritonavir-boosted atazanavir with different types of NRTI-backbones in a large collaboration of prospective cohort studies from the United States and Europe.

2. Methods

2.1. Study population

The HIV-CAUSAL Collaboration has been described elsewhere.[11] Briefly, the collaboration includes several prospective cohort studies from 6 European countries and the United States: UK CHIC (United Kingdom Collaborative HIV Cohort), ATHENA (AIDS Therapy Evaluation in the Netherlands), FHDH-ANRS CO4 (French Hospital Database on HIV-Agence Nationale de Recherches sur le SIDA), Aquitaine (France), SHCS (Swiss HIV Cohort Study), PISCIS (Proyecto para la Informatización del Seguimiento Clinicoepidemiológico de la Infección por HIV y SIDA [Spain]), CoRIS (Cohorte de la Red de Investigación en SIDA [Spain]), VACS-VC (Veterans Aging Cohort Study-Virtual Cohort [United States]), AMACS (Athens Multicenter AIDS Cohort Study [Greece]), UK Register of HIV Seroconverters, ANRS PRIMO and ANRS SEROCO (Agence Nationale de Recherches sur le SIDA [France]), and GEMES (Grupo Espanõl Multicéntrico para el Estudio de Seroconvertores-Haemophilia [Spain]). All cohorts included in the HIV-CAUSAL Collaboration were assembled prospectively and are based on data collected for clinical purposes within national healthcare systems with universal access to care. Each cohort in the collaboration collects all CD4 cell counts, HIV-1 RNAs, treatment initiations, AIDS-defining illnesses, and deaths.

For each individual, follow-up started at the initiation of a 1st-line antiretroviral regimen containing either efavirenz or atazanavir (baseline). Our analysis was restricted to HIV-positive individuals who met the following eligibility criteria at baseline dates between January 2004 and January 2013: age 18 years or older, previously antiretroviral therapy-naive, no history of an AIDS-defining illness,[12] not pregnant (when information was available), and CD4 cell count and HIV-1 RNA measurements within 6 months prior to baseline. For the analysis of clinical outcomes, follow-up ended at the occurrence of the outcome, 12 months after the most recent laboratory measurement (i.e., we considered an individual to be lost to follow-up if and when he had no new CD4 or HIV-1 RNA measurements for 12 months), pregnancy (if known), or the cohort-specific administrative end of follow-up (ranging from September 2010 to March 2013), whichever occurred first. For the analysis of immunologic and virologic outcomes, follow-up ended on average at 12 months after baseline.

2.2. Outcomes

We considered clinical, immunologic, and virologic outcomes. The clinical outcomes of interest were death from any cause and clinical AIDS-defining illness[12] or death. Dates of death were identified using a combination of national and local mortality registries and clinical records as described elsewhere,[11] and AIDS-defining illnesses were ascertained by the treating physicians.

The main immunologic and virologic outcomes of interest were the 12-month change in CD4 cell count after baseline and virologic failure defined as HIV-RNA > 50 copies/mL at 12 months, respectively. Our definition of virologic failure was chosen to allow for comparison with the results from the trials. Although a single measurement of HIV-RNA > 50 copies/mL could be a viral blip as opposed to a failure, our results would only be affected if the frequency of blips varies by antiretroviral regimen. If CD4 cell count or HIV-RNA was not measured exactly 12 months after baseline, we used the closest measurement within 2 months. In secondary analyses, we also studied the CD4 cell count and virologic failure at 24 months.

2.3. Antiretroviral regimens

We considered 2 types of 1st-line regimens: efavirenz and atazanavir regimens. The analysis was restricted to individuals who started an NRTI backbone and either efavirenz or ritonavir-boosted atazanavir at baseline. Individuals were excluded if they started an ineligible drug (i.e., an INSTI, a fusion inhibitor, an NNRTI other than efavirenz, or a PI other than ritonavir/atazanavir) or both efavirenz and atazanavir at baseline.

In our main analysis, we allowed efavirenz or ritonavir-boosted atazanavir to be paired with any NRTI backbone. In subgroup analyses, we included those backbones that appear in the most recent guidelines[1–4] or that were used in the randomized trials.[6,7] Specifically, we focused on the backbones abacavir/lamivudine and tenofovir/emtricitabine.

2.4. Statistical methods

We fit pooled logistic models to estimate the hazard ratio of each clinical outcome for efavirenz versus atazanavir regimens. Both models included a regimen indicator (1: efavirenz, 0: atazanavir), cohort, month of follow-up (modeled as a restricted cubic spline with 4 knots at 1, 6, 24, and 60 months), and the following baseline covariates: sex, age (<35, 35–49, ≥50 years), race (white, black, other or unknown), geographic origin (Western countries, sub-Saharan Africa, other, or unknown), mode of HIV acquisition (heterosexual, homosexual/bisexual, injection drug use, other or unknown), CD4 cell count (<200, 200–299, 300–399, 400–499, and ≥500 cells/mm^3), HIV-1 RNA (<10,000, 10,000–100,000, and >100,000 copies/mL), calendar year (2004–2007, ≥2008), and years since HIV diagnosis (<1, 1–4, ≥5 years or unknown). For the immunologic outcome, we fit a linear regression model with the same covariates to estimate the 12-month change in CD4 cell count for efavirenz versus atazanavir regimens among those with measurements at 12 ± 2 months. For the virologic outcome, we fit a modified Poisson regression model[13] with the same covariates to estimate the risk ratio of virologic failure at 12 months for efavirenz versus atazanavir regimens among those with measurements at 12 ± 2 months.

In the analyses of the immunologic and virologic outcomes, some individuals did not have a measurement during the interval 12 ± 2 months after baseline. To adjust for potential selection bias, we estimated stabilized inverse probability weights[14] of having a measurement via pooled logistic models for artificial censoring that included the time-fixed covariates and time-varying CD4 cell count (<200, 200–299, 300–399, 400–499, and ≥500 cells/mm^3), HIV-1 RNA (<10,000, 10,000–100,000, and >100,000 copies/mL), and month of last laboratory measurement (continuous).

Under the assumption that we measured and successfully adjusted for all confounders, the estimated coefficient for the regimen indicator in the adjusted models is analogous to the "intention-to-treat" effect that would have been estimated from an open-label randomized trial with similar adherence and follow-up. Because we defined the clinical regimens of interest in terms of the 1st-line regimen only, it was unnecessary to adjust for joint determinants of switching and death.

For the 2 clinical outcomes, we also estimated absolute risks by fitting adjusted models like the one described above that also included product ("interaction") terms between the regimen indicator and month of follow-up with spline terms. The predicted values from the models were then used to estimate the 5-year survival and 5-year AIDS-free survival curves from baseline.

2.5. Subgroup and sensitivity analyses

For all outcomes, we compared efavirenz and atazanavir in subgroups defined by baseline calendar year, sex, age, mode of HIV acquisition, baseline CD4 cell count, and baseline HIV-1 RNA.

Because the lower limit of detection was unknown in <5% of observations with HIV-1 RNA between 50 and 400 copies/mL, we conducted a sensitivity analysis in which we defined virologic failure as HIV-1 RNA >400 copies/mL.

In another sensitivity analysis, we allowed a 6-month grace period for individuals to complete one of the regimens of interest as opposed to requiring individuals to start all of the drugs in their regimen simultaneously. Follow-up on individuals was artificially censored if and when they started an ineligible drug before completing a regimen or at 6 months from baseline if their regimen was not yet complete. As previously described, to adjust for potential selection bias due to the artificial censoring, we estimated unstabilized inverse probability weights[14] via pooled logistic models for artificial censoring that included the time-fixed covariates and time-varying CD4 cell count (restricted cubic spline with 5 knots at 10, 200, 350, 500, and 1000 cells/mm^3), HIV-1 RNA (<10,000, 10,000–100,000, and >100,000 copies/mL), AIDS-defining illness (when the outcome was death alone), and time since last laboratory measurement (0, 1–2, 3–4, 5–6, and ≥7 months).

Several other sensitivity analyses were also performed. For all 4 outcomes, we used continuous as opposed to categorical baseline covariates and investigated the effect of including chronic hepatitis C infection[15] as a baseline covariate. For the clinical outcomes, we weighted individuals' contributions to the models by the inverse of their probability of remaining uncensored due to infrequent laboratory measurements. For the immunologic and virologic outcomes, we also weighted by the inverse probability of remaining alive at 12 ± 2 months after baseline as a form of competing risks analysis.

All 95% CIs were estimated via a nonparametric bootstrap with 500 samples. All analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC). The institutional review board at Harvard T.H. Chan School of Public Health approved our research.

3. Results

The dataset included 23,087 individuals of which 4301 followed an atazanavir regimen and 18,786 followed an efavirenz regimen. Table 1 shows the characteristics of the study population by regimen type at baseline. A higher proportion of women, those

Table 1

Characteristics of 23,087 therapy-naive HIV-positive individuals at baseline, HIV-CAUSAL Collaboration 2004 to 2013.

Characteristic		No. of individuals, %					
		Atazanavir (n = 4301)		Efavirenz (n = 18,786)		Total (n = 23,087)	
Sex	Men	3372	(78.4)	16,021	(85.3)	19,393	(84)
	Women	929	(21.6)	2765	(14.7)	3694	(16)
Age, years	<35	1435	(33.4)	6436	(34.3)	7871	(34.1)
	35–50	2035	(47.3)	8883	(47.3)	10,918	(47.3)
	>50	831	(19.3)	3467	(18.5)	4298	(18.6)
Geographic origin	Western countries	3215	(74.8)	13,589	(72.3)	16,804	(72.8)
	Sub-Saharan Africa	601	(14)	2423	(12.9)	3024	(13.1)
	Other	348	(8.1)	1755	(9.3)	2103	(9.1)
	Unknown	137	(3.2)	1019	(5.4)	1156	(5)
Acquisition group	Heterosexual	1444	(33.6)	5118	(27.2)	6562	(28.4)
	Homosexual	1892	(44)	9597	(51.1)	11,489	(49.8)
	Injection drug use	187	(4.3)	492	(2.6)	679	(2.9)
	Other/unknown*	778	(18.1)	3579	(19.1)	4357	(18.9)
CD4 cell count, per mm^3	<200	1226	(28.5)	5246	(27.9)	6472	(28)
	200–299	1245	(28.9)	6124	(32.6)	7369	(31.9)
	300–399	1030	(23.9)	4513	(24)	5543	(24)
	400–499	427	(9.9)	1587	(8.4)	2014	(8.7)
	≥500	373	(8.7)	1316	(7)	1689	(7.3)
HIV-1 RNA, copies/mL	<10,000	827	(19.2)	3473	(18.5)	4300	(18.6)
	10,000–100,000	1958	(45.5)	8805	(46.9)	10,763	(46.6)
	>100,000	1516	(35.2)	6508	(34.6)	8024	(34.8)
Calendar year	2004–2007	1296	(30.1)	6799	(36.2)	8195	(35.5)
	≥2008	3005	(69.9)	11,987	(63.8)	14,892	(64.5)
Cohort	UK CHIC	704	(16.4)	5174	(27.5)	5878	(25.5)
	ATHENA	380	(8.8)	2749	(14.6)	3129	(13.6)
	FHDH-ANRS CO4	1491	(34.7)	2778	(14.8)	4269	(18.5)
	Aquitaine	322	(7.5)	916	(4.9)	1238	(5.4)
	SHCS	421	(9.8)	2094	(11.1)	2515	(10.9)
	PISCIS/AMACS	182	(4.2)	1609	(8.6)	1791	(7.8)
	CoRIS	152	(3.5)	658	(3.5)	810	(3.5)
	Seroconverters†	553	(12.9)	2646	(14.1)	3199	(13.9)
	VACS-VC	96	(2.2)	162	(0.9)	258	(1.1)
Hepatitis C infection	Definite/Probable	116	(2.7)	557	(3)	673	(2.9)
	Possible	139	(3.2)	467	(2.5)	606	(2.6)
	None	4046	(94.1)	17,762	(94.5)	21,808	(94.5)

AMACS = Athens Multicenter AIDS Cohort Study, ANRS = Agence Nationale de Recherches sur le SIDA, ATHENA = AIDS Therapy Evaluation in the Netherlands, CoRIS = Cohorte de la Red de Investigación en SIDA, FHDH = French Hospital Database on HIV, GEMES = Grupo Español Multicéntrico para el Estudio de Seroconvertores-Hemofilia, HIV = human immunodeficiency virus, PISCIS = Proyecto para la Informatización del Seguimiento Clinicoepidemiológico de la Infección por HIV y SIDA, SHCS = Swiss HIV Cohort Study, UK CHIC = United Kingdom Collaborative HIV Cohort, VACS-VC = Veterans Aging Cohort Study-Virtual Cohort.

* Other/Unknown acquisition group included all VACS-VC participants.

† Includes the UK Register of HIV Seroconverters, ANRS PRIMO, ANRS SEROCO, and GEMES cohorts.

Table 2

Clinical and virologic outcomes by recommended nucleoside reverse transcriptase inhibitor backbone for regimens based on efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013.

Backbone	No. of individuals/ No. deaths/No. of AIDS or deaths		Death	AIDS or death	Virologic failure
	Atazanavir	Efavirenz	Hazard ratio*,† (95% CI)	Hazard ratio*,† (95% CI)	Risk ratio*,‡ (95% CI)
All backbones	4301/83/157	18,786/389/825	0.98 (0.77, 1.24)	1.09 (0.91, 1.30)	0.80 (0.74, 0.86)
Abacavir/lamivudine	658/9/23	1629/38/85	2.52 (1.04, 6.10)	1.71 (0.99, 2.94)	0.76 (0.58, 0.98)
Tenofovir/emtricitabine	3286/43/96	14,247/218/479	1.16 (0.82, 1.63)	1.15 (0.91, 1.45)	0.77 (0.70, 0.85)
Abacavir/lamivudine and tenofovir/emtricitabine	3944/52/119	15,876/256/564	1.23 (0.90, 1.67)	1.17 (0.96, 1.42)	0.77 (0.70, 0.83)

AIDS = acquired immune deficiency syndrome, CI = confidence interval, HIV = human immunodeficiency virus, No. = number.

* Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV-1 RNA, calendar year, and years since HIV diagnosis).

† Hazard ratio of efavirenz versus atazanavir.

‡ Risk ratio of efavirenz versus atazanavir based on 2878 and 13,643 individuals with HIV-1 RNA measurements at 12 ± 2 months in the atazanavir and efavirenz groups, respectively.

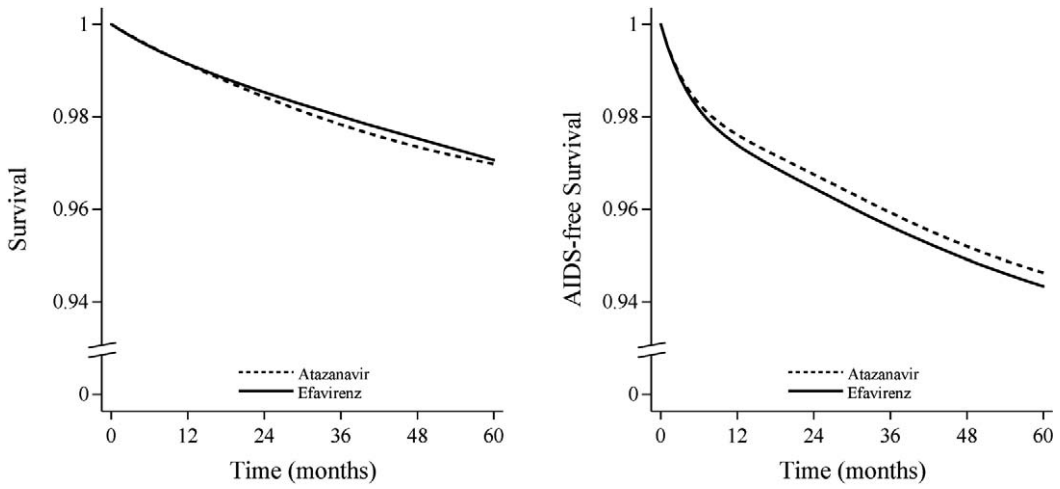


Figure 1. Survival (left) and AIDS-free survival (right) for efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013. The curves are standardized by the baseline covariates listed under Table 2.

who acquired HIV through heterosexual transmission, and those starting treatment in 2008 or later, initiated atazanavir than efavirenz.

As shown in Table 2, 83 individuals died and 157 developed an AIDS-defining illness or died among those initiating an atazanavir regimen, and 389 individuals died and 825 developed an AIDS-defining illness or died among those initiating an efavirenz regimen. In the mortality analysis, the median (interquartile range) follow-up time was 27 (14, 45) months for the atazanavir regimens and 32 (17, 52) months for the efavirenz regimens. A total of 956 (22%) individuals following an atazanavir regimen and 4617 (25%) following an efavirenz regimen were lost to follow-up. The numbers were similar in the AIDS or death analysis. Compared with atazanavir, the hazard ratio (95% CI) for efavirenz was 0.98 (0.77, 1.24) for death and 1.09 (0.91, 1.30) for AIDS or death.

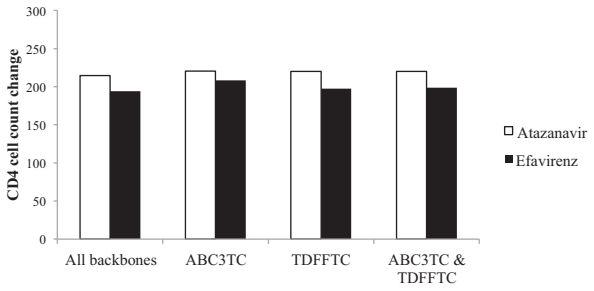
Figure 1 plots the estimated 5-year survival and 5-year AIDS-free survival with all backbones. The 5-year survival was 96.9% (96.3%, 97.6%) for the atazanavir regimens and 97.0% (96.7%, 97.4%) for the efavirenz regimens. The survival difference was 0.1% (−0.7%, 0.8%) at 5 years. The 5-year AIDS-free survival proportion was 94.6% (93.7%, 95.5%) for the atazanavir regimens and 94.3% (93.9%, 94.7%) for the efavirenz regimens. The AIDS-free survival difference was −0.3% (−1.2%, 0.6%) at 5 years.

Table 2 also provides the risk ratios of virologic failure at 12 ± 2 months comparing efavirenz with atazanavir. Among those initiating atazanavir and efavirenz regimens, 683/2878 (24%) and 2644/13,643 (19%) had HIV-1 RNA >50 copies/mL at 12 months, respectively. Compared with atazanavir, the risk ratio of virologic failure at 12 months for efavirenz was 0.80 (0.74, 0.86). Results were similar in subgroups defined by backbone. Among those initiating atazanavir and efavirenz regimens, 19% and 15% had HIV-1 RNA >50 copies/mL at 24 months, respectively. Compared with atazanavir, the risk ratio of virologic failure at 24 months for efavirenz was 0.81 (0.74, 0.89).

Figure 2 shows the 12-month adjusted mean change in CD4 cell count by backbone. Compared with atazanavir, the estimated mean change in CD4 cell count (95% CI) for efavirenz was −20.8 (−27.8, −13.9) for all backbones. The mean CD4 cell count would have increased from 280 to 495 cells/mm^3 over 12 months had all individuals taken an atazanavir regimen, and from 280 to 474 cells/mm^3 had all individuals taken an efavirenz regimen. Results were similar in subgroups defined by backbone. Compared with atazanavir, the estimated mean change in CD4 cell count over 24 months (95% CI) for efavirenz was −15.6 (−25.3, −5.9).

Most individuals initiated a backbone of either abacavir/lamivudine (10%) or tenofovir/emtricitabine (76%). Abacavir/lamivudine was used more frequently with atazanavir, while tenofovir/emtricitabine were used equally with atazanavir and efavirenz. In the subgroup of individuals using 1 of these 2 backbones, the hazard ratio for efavirenz was 1.23 (0.90, 1.67) for death and 1.17 (0.96, 1.42) for AIDS or death (Table 2).

None of the sensitivity analyses yielded appreciably different results (data not shown). In subgroup analyses, estimates for all 4 outcomes were similar when we restricted to baseline years 2008 and beyond, men, those aged less than 50 years, noninjection drug users, those with baseline CD4 cell counts below 350 cells/mm^3, those with baseline viral loads above 100,000 copies/mL, and those from Western countries. When we defined virologic



ABC = abacavir, 3TC = lamivudine, TDF = tenofovir, FTC = emtricitabine

Figure 2. Immunologic outcomes by recommended NRTI backbone for regimens based on efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013. 3TC = lamivudine, ABC = abacavir, FTC = emtricitabine, HIV = human immunodeficiency virus, NRTI = nucleoside reverse transcriptase inhibitor, TDF = tenofovir.

failure as HIV-1 RNA >400 copies/mL, the percentage with virologic failure decreased, but the risk ratio comparing efavirenz with atazanavir remained similar. Finally, allowing a 6-month grace period for individuals to complete one of the regimens of interest had little effect on the estimates.

4. Discussion

The clinical effectiveness of efavirenz versus ritonavir-boosted atazanavir has not been directly studied in randomized trials, which have focused on short-term immunologic and virologic outcomes. Our study compared efavirenz versus atazanavir regimens with respect to clinical outcomes among antiretroviral-naive, AIDS-free individuals in Europe and the United States. We did not detect any differences in mortality or AIDS-defining illness.

We also found that individuals on efavirenz regimens were 20% less likely to have virologic failure at 12 months as those on atazanavir regimens and experienced a smaller 12-month increase in CD4 cell count by 20.8 cells/mm^3. This absolute difference in CD4 cell count was small and of questionable clinical relevance, especially for greater than 450 cells/mm^3 CD4 cell counts that are expected in our study at 12 months.

Our virologic and immunologic findings were consistent with those of the 2 previous trials.[6,7] The Altair Study found that the mean change in CD4 cell count was 5 cells/mm^3 higher in the atazanavir arm than in the efavirenz arm over 48 weeks. The A5202 study estimated the median change in CD4 cell count and found a 10 cells/mm^3 greater increase in the efavirenz arm when a backbone of abacavir/lamivudine was used and a 12 cells/mm^3 smaller increase in the efavirenz arm when a backbone of tenofovir/emtricitabine was used compared with the atazanavir arm. Like in our study, these differences were small and of little clinical relevance. The A5202 study found advantages of efavirenz over atazanavir with respect to virologic failure at 48 weeks, but little association was found in the Altair study.

Our estimates are based on less restrictive inclusion criteria, and therefore are potentially more relevant to the general population of HIV-infected individuals than those of the trials. Specifically, both trials restricted to individuals with baseline HIV-1 RNA ≥ 5000 copies/mL and included some individuals who were not AIDS-free at baseline. The trials also excluded those with low CD4 cell counts (Altair study: 50 cells/mm^3, A5202 study: 100 cells/mm^3 if prior AIDS, 75 cells/mm^3 if not prior AIDS). When we restrict to individuals with baseline HIV-1 RNA ≥ 5000 copies/mL, CD4 ≥ 50 cells/mm^3, and to one of the backbones used in the trials, the 12-month adjusted mean change in CD4 cell count for efavirenz versus atazanavir was −22.8 (−30.5, −15.1) and the risk ratio of virologic failure at 12 months for efavirenz versus atazanavir was 0.77 (0.71, 0.85). We compared these estimates to those from a meta-analysis we conducted with the published information in the 2 trials. This virologic result was not as strong as the result of the meta-analysis: 0.65 (0.49, 0.85). Unfortunately, we were unable to conduct a meta-analysis using the available information for CD4 cell count change.

In the Altair study, both arms had a backbone of tenofovir/emtricitabine. In the A5202 study, both arms had a backbone of either tenofovir/emtricitabine or abacavir/lamivudine. In our main analysis, any backbone could be used. We also conducted analyses restricted to the backbones used in the trials. Results in subgroups defined by backbone were similar to those for all backbones with the exception of the clinical outcomes when abacavir/lamivudine was used. However, these results were based on few events and confidence intervals were wide.

Like all observational estimates, ours rely on the untestable assumption that we have successfully measured and adjusted for all confounders. In this analysis, we measured and adjusted for sex, age, race, geographic origin, mode of HIV acquisition, CD4 cell count, HIV-1 RNA, calendar year, and years since HIV diagnosis. If further adjustment is necessary to account for confounding factors responsible for large prognostic differences between patients initiating efavirenz versus atazanavir, the assumption would not hold.

One of these confounding factors might be adherence. Atazanavir was independently associated with suboptimal adherence in a study of individuals from the SMART study.[16] Atazanavir also has a higher genetic barrier to resistance than efavirenz.[7] These facts may suggest that atazanavir was more often prescribed to individuals whose future adherence was questionable (e.g., because of markers of poor health such as cardiovascular disease). However, we measured and adjusted for several proxies for adherence, including HIV-1 RNA, calendar year, intravenous drug use, years since HIV diagnosis, and time since last laboratory measurement.

In addition, during the course of this study, both drugs may have been used in a way that is no longer considered optimal. Efavirenz is contraindicated for patients with psychiatric illness and pregnant women, while ritonavir-boosted atazanavir is not recommended for use with antacids and other drugs that raise gastric pH.[2] Although our data did not allow us to investigate psychiatric illness or the use of nonantiretroviral drugs, we excluded women known to be pregnant in all analyses. The magnitude of the reported association makes it unlikely that our immunologic and virologic estimates can be fully explained by the use of antacids, anti-psychotics, or other drugs.

In summary, our findings extend those of randomized trials from immunologic and virologic outcomes to clinical outcomes. Our findings do not support changes to the current clinical guidelines for HIV-positive individuals, but the new evidence presented here may be informative to those drafting the next set of guidelines. Future studies need to consider the effects of efavirenz and atazanavir on other clinical outcomes including non-AIDS-defining illnesses, when paired with specific backbones and over longer periods. This is particularly true in resource-limited settings and other areas where efavirenz and atazanavir are needed as antiretroviral therapy alternatives.

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